

SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

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Why did cigarette sales
decline in Japan?

The story of
THS in Japan



JAPAN

日本

HARM

REDUCTION:

**A FOCUS ON
JAPAN**

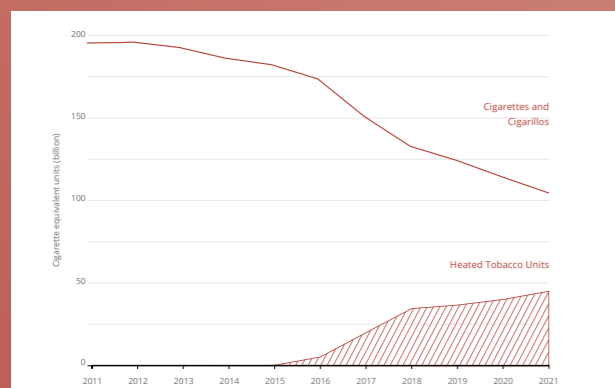


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INTRODUCTION

In this issue of the Scientific Update, we hit again on the topic of real-world evidence by exploring in-depth examples of tobacco harm reduction success that can be found in Japan. We have mentioned in several past issues the decline in cigarette sales in Japan, which is likely caused by the introduction of heated tobacco products. In this issue, we cover that again in greater detail. We also talk with Tomoko Iida, Director Regional Scientific Engagement Asia. She gives us an in-depth view on the impact that our leading heated tobacco product has on tobacco harm reduction in Japan as well as on the local research and scientific communications that help make that impact possible.

Tobacco harm reduction is a global imperative, but what works well in that context for one country might need to be adapted to succeed in another. We hope that readers could find inspiration in the research discussed here and advance tobacco harm reduction in ways that work for them and their country.



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EVENTS

GLOBAL FORUM ON NICOTINE

Global Forum on Nicotine

📍 Warsaw, Poland/Online

📅 June 16-18, 2022

Four PMI scientists participated in this year's Global Forum on Nicotine (GFN) by submitting GFN Fives – 5-minute pre-recorded multimedia presentations. Markus Nordlund discussed "Combustion differentiating criterion for novel tobacco and nicotine products." Diego Marescotti's presentation was titled "Adverse outcome pathway (AOP) for human health risk assessment" and Meagan Antunes presented our work on real-world evidence. Ondrej Koumal discussed "Insights on the impact of the introduction of heated tobacco products in Japan on sales of cigarettes and the smoking prevalence."

[Watch the presentations from PMI scientists at GFN](#)

OPEN SCIENCE

Open Science, Live from the Cube

📍 Neuchâtel, Switzerland/Online

📅 June 20, 2022

Our seventh Open Science event was held live in June at our R&D Center, The Cube, in Neuchâtel, Switzerland. It focused on the concept of tobacco harm reduction and the role scientifically substantiated smoke-free products can play in complementing existing tobacco control measures. Our scientific experts, Dr. Gizelle Baker and Dr. Markus Nordlund, and physician and medical oncologist, Dr. Peter Harper, took part in a panel discussion and a question-and-answer session. Topics included why the absence of combustion is an important first step in a harm reduction approach to smoking and the science behind our smoke-free alternatives. Participants also attended virtually on our Open Science platform and on [LinkedIn](#).

Watch the replay [here](#).

OPEN SCIENCE

Open Science in Brief: A focus on real-world evidence

📍 Online, LinkedIn

📅 September 20, 2022

Our eighth Open Science event, Open Science in Brief, was held virtually only on LinkedIn in September. Dr. Angela van der Plas, Manager Real-World Evidence & Epidemiology, presented some of the data we have gathered based on real-world evidence. She also answered questions we received during previous Open Science events and took part in a live chat during the session.



SCIENTIST HIGHLIGHT



Meagan Antunes

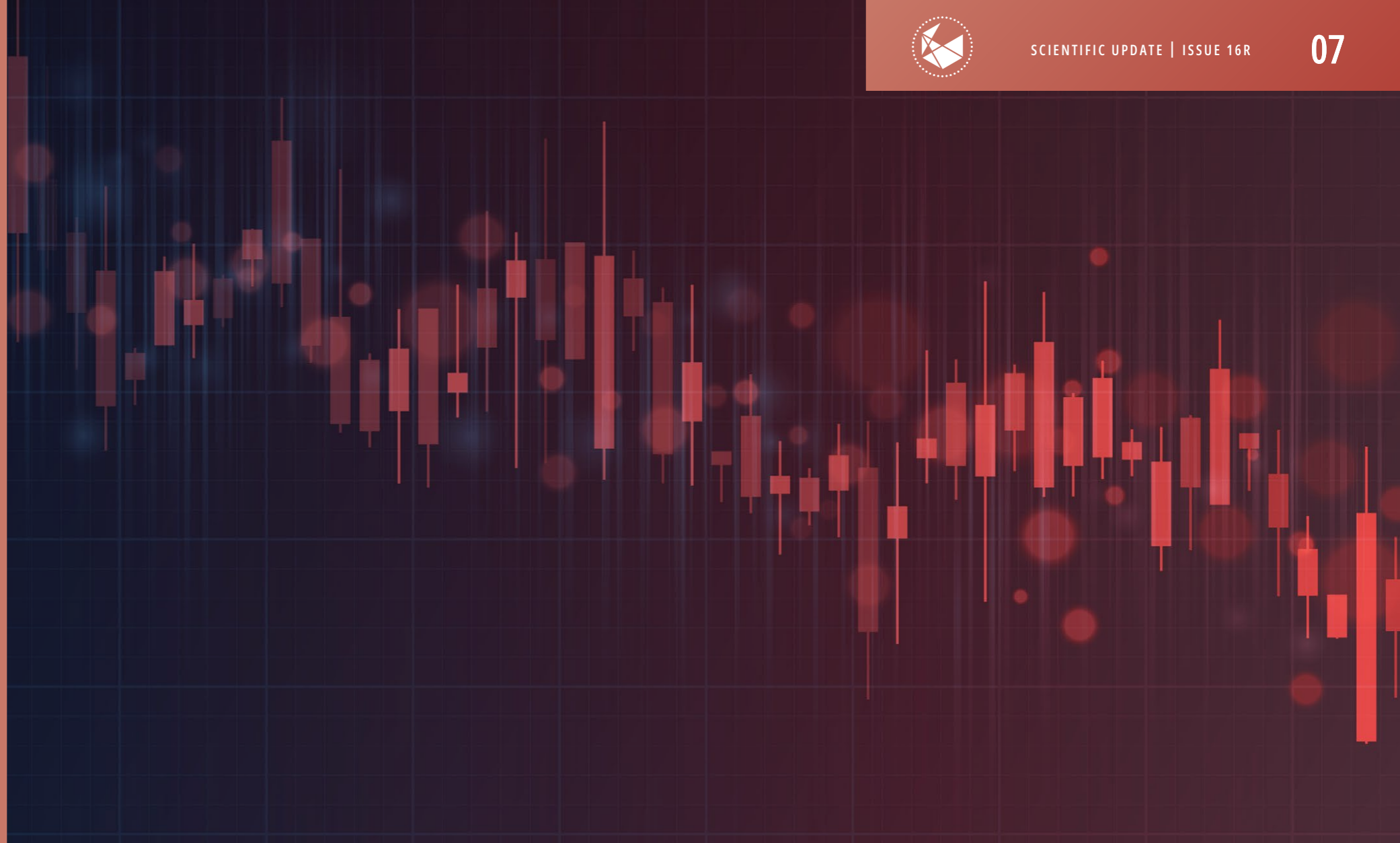
Meagan first joined PMI in 2021 as an intern in Live Sciences before joining as a scientist specializing in real-world evidence and epidemiology. She holds a master's degree in Bioinformatics and Computational Biology from the University of Bern, and a BSc in Mathematical Biology from Queens University, Canada. Meagan has a keen interest in biostatistics, data analysis, programing, literature reviews, and scientific writing.

In June 2022, Meagan was one of several PMI authors on a study on the topic of real-world evidence, which she also presented in a GFN Five at the Global Forum on Nicotine. Meagan loves working with data and coding, and running analyses is her favorite part of project work. During her studies at Queens University, she provided one-to-one mentorships in mathematics and statistics to first- and second-year students.



WHY DID CIGARETTE SALES DECLINE IN JAPAN?

Scientifically substantiated smoke-free alternatives for adults who would otherwise continue to smoke can play a key role in harm reduction, and the Tobacco Heating System (THS) is our leading smoke-free alternative. Japan is the first country where our THS was launched, and it remains the country with the highest number of heated tobacco product (HTP) users in the world. Here, we examine whether the introduction of HTPs and specifically our THS in Japan resulted in the decline of cigarette sales in Japan.



Tobacco harm reduction

Reducing tobacco-related harm at the population level by introducing less harmful smoke-free alternatives depends not only on the reduction in risk to the individual who switches from cigarettes to such a product, but also its adoption by adult smokers.

According to the harm reduction equation, the more adult smokers who choose the lower risk options instead of continuing to smoke cigarettes, the bigger the impact on reducing population harm.

Heated tobacco products, or HTPs, heat the tobacco just enough to release a nicotine-containing tobacco aerosol but without burning the tobacco. Because tobacco is heated and not burned there is no smoke, and the levels of harmful and potentially harmful chemicals in the generated aerosols can be significantly reduced compared to cigarette smoke.

Because of this they have the potential to be less harmful to continued smoking. Whether this is the case, should be assessed for each particular product.

The totality of the evidence available today from our rigorous scientific assessment program indicates that switching completely to our Tobacco Heating System (THS), while not risk-free, presents less risk of harm than continued smoking.

THS, commercialized as *IQOS*, has the potential to help adult smokers switch away from combustible cigarettes - the most harmful use of tobacco. In fact, independent studies have explored the relationship between a decline in cigarette sales and the introduction of the THS in Japan from 2014 to 2016.

A 9.5% average annual decline in cigarette sales from 2015 to 2018 in Japan

The THS was introduced in Nagoya, Japan, in late 2014 as a city-pilot and launched nationwide in 2016. The HTP had a staggered introduction across Japan over time, producing a detailed set of statistics to analyze.

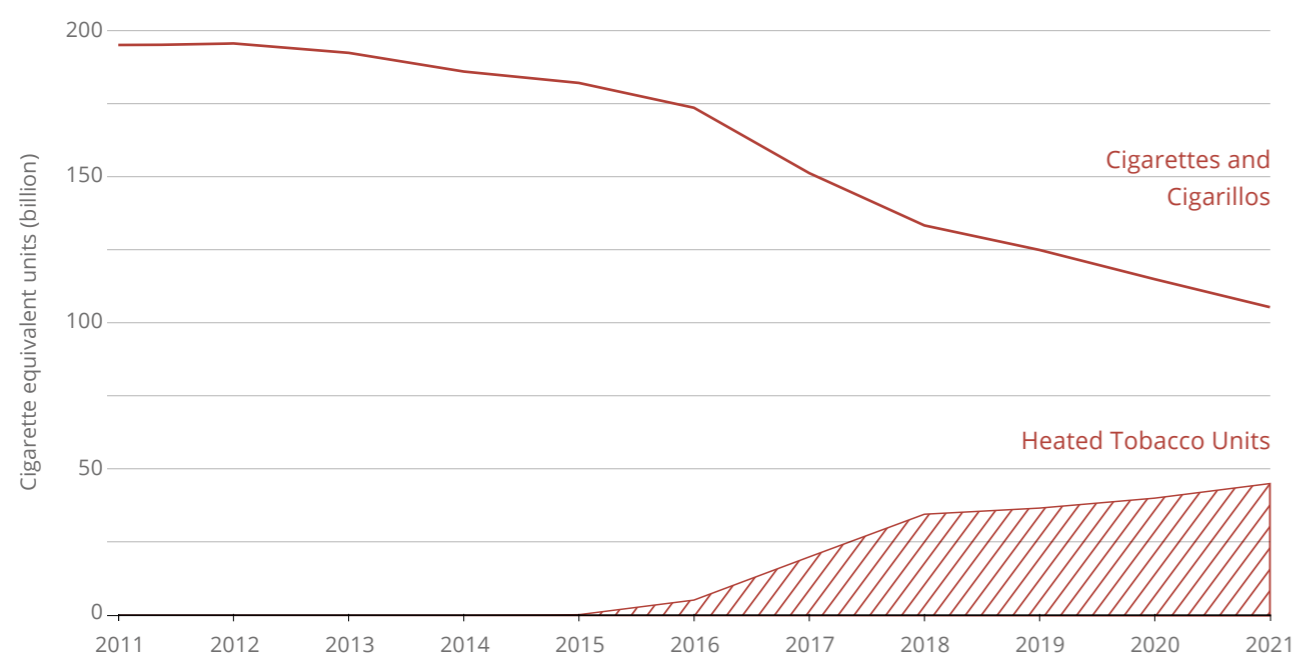
Following the HTP's introduction from 2015-2016, cigarette sales began to substantially decline in each of the Japanese regions. Before this nationwide launch, total tobacco sales in Japan declined at a rate of 1.8% on average between 2011 and 2015. After the launch of the HTP in Japan, total tobacco sales continued to follow that same trend. But notably, the sale of cigarettes fell more sharply after the nationwide launch of the HTP: a 9.5% average annual decline from 2015 to 2018.

Researchers working for the American Cancer Society [published research in the British Medical Journal's Tobacco Control](#). They analyzed per capita cigarette sales data from retailers to examine the cause of the significant decline in cigarette sales. The study covered 11 of Japan's 12 regions, representing 99% of the country's population, and 72% of all cigarette sales relative to the data reported by Euromonitor International. The data was collected from retail outlets within these 11 regions based on sales data from 2014 to 2018.

Besides the launch of the HTP, the authors investigated other potential causes for the decline, such as pricing, stricter regulations, the availability of competing HTPs, or even just chance. To do so, they applied multiple alternative causation models to the sales figures. The researchers determined that those factors were unlikely to be the main causes of the decline in cigarette sales.



In-market sales volume of cigarettes, cigarillos, and Heated Tobacco Units, Japan, 2011-2021



In-market sales volume of cigarettes, cigarillos, and HTUs, Japan, 2011-2021 PMI Integrated Report 2021 case study: Association between the introduction of heated tobacco products and declines in cigarette smoking

THS introduction is the most likely explanation for faster cigarette sales decline in Japan

The authors concluded that the introduction of the HTP was the most likely explanation for the decline in cigarette sales in Japan. And further, the downward trend of combined tobacco sales continued even after the launch of the HTP. We can interpret this to mean that the launch of this product did not lead to an increase in overall tobacco consumption, and that many smokers, who would have otherwise continued to smoke cigarettes, have switched to the HTP.

The study only included sales data, and therefore, could not assess risk or harm reduction, the authors noted. But, citing other third-party research, they added,

Studies that examine exposures of known toxins in IQOS aerosol have generally found substantially lower levels than in conventional cigarette smoke.

The authors wrote, "Definitively identifying that the introduction of a novel tobacco product is significantly changing the marketplace for tobacco products is important information for policymakers and public health proponents as they consider how to alter existing tobacco control policies to accommodate these new products."



Another independent study further supports the role of THS in cigarette sales decline in Japan

An [article](#) published by researchers at the Medical University of South Carolina and at the University of Ottawa explored the relationship between the decline in cigarette sales in Japan between 2011 and 2019 and the introduction of HTPs into the Japanese market in late 2015. Data for this study came from the Tobacco Institute of Japan and publicly available data from Philip Morris International (PMI).

Like the research described above, this study found that the acceleration in the decline in cigarette sales in Japan since 2016 does, in fact, correspond to the 2015 introduction and growth of sales of HTPs in the country. Between 2011 and 2019, overall cigarette sales fell by 38% and total tobacco sales (i.e., combining cigarettes and HTPs) declined by 19%. Following the introduction of HTPs into the Japanese market between 2016-2019, the annual percent change (APC) for tobacco sales overall was -4.77% between 2011 and 2019 (a negative APC means that the sales dropped over time). However,

separating out cigarette only sales from HTP sales revealed a different pattern. The APC for cigarette only sales was -3.10% between 2011 and 2015, and -16.38 % between 2016 and 2019, a significant drop in cigarette sales after the introduction of THS.

The authors noted that their work did not address whether cigarette smokers were completely substituting one product for another, just that the data indicates that HTPs have accelerated the decline in cigarette sales. In fact, we can better understand product use patterns by examining separate data from the Japanese government's National Health and Nutrition Survey. This showed that the most frequent pattern of use of HTPs in Japan is exclusive use, with an overwhelming majority of HTP users, 76% in 2019, not reporting any cigarette smoking. The proportion of regular smokers who smoked both cigarettes and HTPs was 6.9% of men and 4.8% of women.





THE STORY OF THS IN JAPAN

AN INTERVIEW WITH TOMOKO IIDA



Tomoko Iida is Director, Regional Scientific Engagement Asia at PMI. Prior to this role, she was the Director of External and Scientific Affairs in Japan, helping to oversee the introduction of our Tobacco Heating System (THS), commercialized as IQOS, in the country.

What impact has the introduction of the THS had on tobacco harm reduction in the country?

In 2000, approximately 47.4 % of men and 33% of all adults in Japan smoked cigarettes. But in 2015, during and after the introduction of the THS, sales of cigarettes began declining five times faster than in preceding years, an average annual decline of 9.5%, according to researchers of the [American Cancer Society study](#). When we look at the data ourselves, we can also clearly see that even after heated tobacco products (HTPs) became available, sales of all tobacco products (including both HTPs and conventional cigarettes) continued to fall. Data from the 2019 [National Health and Nutrition Survey](#) (surveys were not conducted during the pandemic) indicates that 76% of consumers who use HTPs do so exclusively. Only 24% of HTP users continued to smoke cigarettes. HTP use in Japan has also had a minimal impact on unintended users – nonsmokers, former smokers, and [adolescents](#).

Why was Japan among the first countries where the THS was launched and what made it such a good initial market?

The uniqueness of Japan comes across through societal values of hygiene, cleanliness, and courtesy as well as through interest and adoption of new technologies and innovations. Consumer preference for HTPs compared to cigarettes was shown through our consumer testing and research. HTPs were considered to have a significant advantage over cigarettes because of some of the key features that had a cultural fit with Japanese smokers, especially in the early days. For example, HTPs do not generate ash (no need for anyone to clean ashtrays), no fire (mitigates the risk of household fires), less smell, and no smoke (bothers others less).

How can Japan serve as an example of successful tobacco harm reduction to other countries?

The experience and data from Japan show that smoke-free products can play a significant role in tobacco harm reduction and public health. Sales and prevalence data from Japan continues to show that HTPs have had a positive impact on decreasing smoking prevalence by transitioning a large number of adult smokers away from smoking cigarettes. The uptake of HTPs in Japan has also been accompanied by sharp declines in cigarette sales. According to the latest industry report from the Tobacco Institute of Japan, cigarette consumption decreased by 44% in 5 years after the introduction of the THS – the highest decline that Japan has ever had.

Of course, you must consider disposable income, users' preference, and the regulatory environment to address the need for the right product for the country at the right time, but the Japanese experience can certainly be replicated in other countries. Sweden is another example, which came before the harm reduction story in Japan. It has been reported that the use of snus played an important role in [decreasing smoking prevalence](#) in the country, especially among men, and a lower rate of lung cancer and heart attacks among men in the country was observed. You have to have the right product to help smokers who won't quit to switch.

Tell us about some of the research PMI has conducted in Japan.

The passive exposure [study](#) is one of several important research studies PMI has conducted in Japan to assess the impact of THS use in real-life settings on users and non-users of the product.

This study exposed nonsmokers to THS aerosol in a restaurant in Tokyo. Urine samples were taken before and after to determine the presence of harmful chemicals in the body. The results showed that the use of THS didn't generate environmental smoke and had no adverse effects on indoor air quality. Also, nonsmokers didn't have an increase in exposure to nicotine and tobacco-specific nitrosamines (TSNA) as a result of passive exposure to the THS aerosol.

The Ministry of Health (MOH) conducted its own studies and concluded that the *"results do not negate the inclusion of HTPs within a regulatory framework for indoor tolerable use from exposure to HTP aerosol, unlike cigarette smoke"*. The revised Health Promotion Law imposed new regulations on smoking cigarettes in small premises. In larger establishments, smoking is allowed only in a dedicated smoking booth, in which eating and drinking are not permitted. However, HTPs may be used in dedicated HTP areas, in which eating and drinking are also allowed.

Another important study was conducted in Tokyo and Fukuoka. This clinical study showed that scaling and root planning in periodontitis patients was beneficial to patients who smoked or who had switched to THS, but the [outcomes among periodontitis patients who switched to THS were better at sites with higher initial probing depth](#).

There are several other studies, some of which are shown on the infographic map of Japan.





Tell us more about independent research. What do Japanese researchers say about heated tobacco/THS?

There are four important independent studies that I'd like to mention here that were carried out by the Ministry of Health, Labour and Welfare (MHLW) of Japan and its affiliated institutions. In a reduced emission study published in the [Journal of UOEH](#), the National Institute of Public Health (NIPH) concluded that "The concentrations of nicotine in tobacco fillers and the mainstream smoke of IQOS were almost the same as those of conventional combustion cigarettes, while the concentration of TSNAs was **one fifth** and CO was **one hundredth** of those of conventional combustion cigarettes."

MHLW and the [National Cancer Center](#) (NCC) conducted two studies to examine the impact of HTPs on indoor air quality. They found that the "exposure to aerosol from HTPs in a designated smoking room under usual conditions is estimated to be tolerable since the lifetime cancer risk is expected to be below a VSD of 10^{-5} (1/100,000), which is three orders of magnitude lower than that for cigarettes smoked under the same conditions".

Research by the Health Service Division, Health Service Bureau, MHLW, published in the [International Journal of Environmental Research and Public Health](#) compared the concentration of nicotine and particulate matter (PM^{2.5}, particles that are 2.5 microns or less in diameter) in the air following 50 puffs from HTPs or cigarettes in a small shower cubicle. They found that the "results do not negate the inclusion of HTPs within a regulatory framework for indoor tolerable use from exposure to HTP aerosol, unlike cigarette smoke".

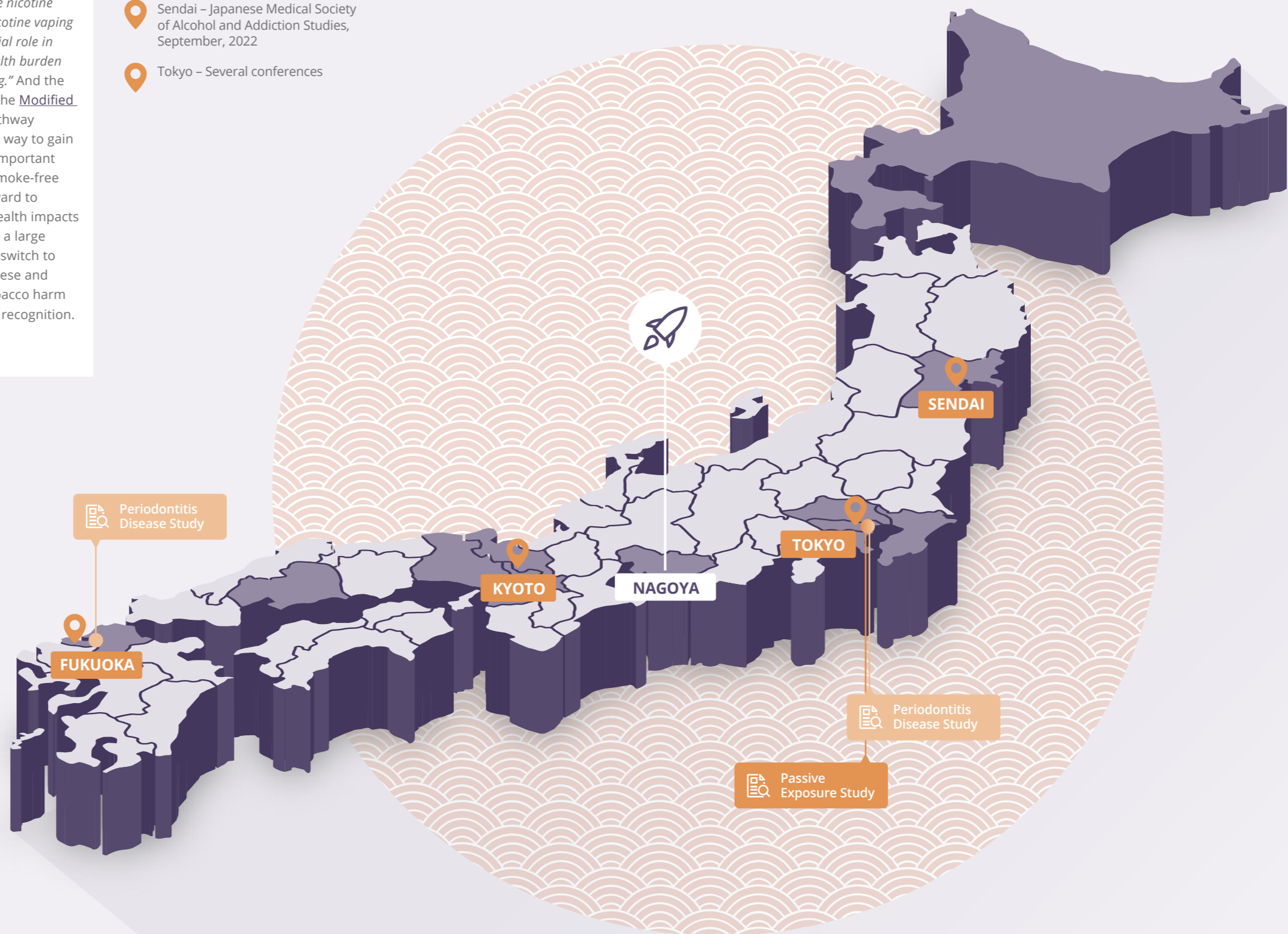
Finally, [research data from Tottori University](#) commissioned by MHLW demonstrates low levels of HTP use by young people, both in absolute and relative terms, compared to combustible cigarettes.

Any last thoughts?

Even though the focus here is on Japan, it's not the only country that is embracing tobacco harm reduction. For example, [Public Health England has stated](#) that "Alternative nicotine delivery devices, such as nicotine vaping products, could play a crucial role in reducing the enormous health burden caused by cigarette smoking." And the U.S. FDA has established the [Modified Risk Tobacco Products](#) pathway which allows companies a way to gain authorization to provide important information about their smoke-free products. I'm looking forward to seeing what population health impacts we will see – if and when - a large number of adult smokers switch to smoke-free products in these and other countries where tobacco harm reduction is gaining more recognition.

Research conferences where PMI presents

-  Kyoto – Science and Technology in Society Forum, October, 2021
-  Fukuoka – 6th Congress of Asian College of Neuropsychopharmacology, October, 2019
-  Sendai – Japanese Medical Society of Alcohol and Addiction Studies, September, 2022
-  Tokyo – Several conferences





PMI PUBLICATIONS

A 3-year study on prevalence and use patterns of THS in Japan

This [paper](#), published in F1000 Research and awaiting peer review, examines the nationwide prevalence and patterns of tobacco and/or nicotine-containing product (TNP) use in Japan between 2016 and 2019 following the introduction of Philip Morris International's (PMI's) Tobacco Heating System or THS on the Japanese market. Cross-sectional surveys were conducted over three study years (2016/2017, 2017/2018, and 2018/2019) in representative samples of the Japanese general adult population and samples of Japanese adult THS users registered in the database of PMI's affiliate in Japan.

PMI authors found that across the three study years, the prevalence of overall current TNP use and overall TNP use by age and sex remained similar, while there was a growing shift from cigarette smoking to smoke-free TNP use. While the prevalence of cigarette smoking declined from 17.6% to 16.0%, the use prevalence of smoke-free TNPs increased, including THS (from 1.8% to 3.3%) and e-cigarettes (from 0.7% to 2.0%). At the same time, TNP initiation, relapse, and re-initiation with THS were all very low across the three study years. Moreover, the majority of adult THS users were exclusive THS users.

The results suggest that current THS use behavior trends are in line with the principles of tobacco harm reduction and that HTPs are effective tools for complementing current tobacco control measures.

Risk perceptions of THS compared to cigarettes change over time

This [study](#) assessed the temporal trends in the relative risk perception (RP) of the Tobacco Heating System (THS) compared to the RP of cigarettes, among current adult THS users in Germany (2018–19), Italy (2018–19), and Japan (2016–17, 2017–18, and 2018–19). It also examined the association between THS use behaviors and relative RP. Risk perception is a key factor for smokers deciding to switch from cigarettes to smoke-free tobacco or nicotine-containing products (TNPs).

PMI researchers analyzed repeated cross-sectional data from online surveys in these countries among a random sample of current adult THS users. The health RPs of cigarettes and THS were assessed using [PMI's ABOUT™–Perceived Risk Instrument](#), and their difference was described as the relative RP of THS to cigarettes.

The study found that the RP of THS is lower than that of cigarettes across the surveyed countries and years and appears to be declining over time. This decline follows the temporal changes observed for other smoke-free products such as e-cigarettes. Further research is needed on the factors that influence the changes in RP over time across countries with varying public health policies and regulations. This would enable them to evaluate the impact of public health policies and external communications on RP, the authors wrote.

Effects of THS on periodontitis treatment outcome

In this [study](#), PMI scientists conducted a 6-month randomized clinical study in Japan to analyze the impact of exposure to the aerosol of the Tobacco Heating System (THS) on periodontitis treatment outcome. Periodontitis, the inflammation of the gums or tissue around the teeth, can cause gum shrinkage and loosening of the teeth. In this study, smokers with generalized periodontitis were randomly assigned to continue smoking or to switch to THS. Then, they had scaling and root planning (SRP) for up to eight weeks and had dental assessments at 3- and 6-month time points.

The study showed that the SRP improved the course of the periodontitis in both cigarette smokers and THS users. THS users showed a trend toward more favorable outcomes in some of the measures in the assessments, however, there was no statistically significant difference between the two groups in this study. The beneficial effects of this treatment might mask the favorable changes that may occur upon modifying one of the several risk factors for periodontitis, cigarette smoking.

A pragmatic approach to toxicology studies on flavorings

Flavor ingredients are often used in smoke-free products, such as e-vapor products. Most are generally recognized as safe for use in food, but there is limited information on their long-term health effects when delivered via inhalation. While it's important to understand the effects of inhalation of these chemicals, the large number of individual ingredients make it impractical to assess them all via conventional means.

In [this paper](#), PMI researchers propose a pragmatic approach, where flavor ingredients are assigned to groups with similar chemical structure, called flavor groups. Representatives of these flavor groups are then selected and tested both individually and as a group in cell culture and laboratory models. This proposal is based on the concept that compounds with similar chemical structures should have comparable metabolic and biological activity. The authors also provide a case study as well as a stepwise description of the approach.

Once completed, this flavor group representative approach could significantly reduce the time and resources required for filling the data gap in understanding the health risks of many flavor ingredients while also minimizing the need for laboratory animals.





PMI SCIENCE

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Important information

This Scientific Update provides an overview of the most recent scientific developments behind PMI's approach to achieving a smoke-free future through a range of alternatives to cigarettes that do not burn tobacco.

The following pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as independent research and government reports.

More detailed information can be found at www.pmiscience.com.